REMARKS

Claims 1-9 are pending and under consideration in the instant application. With this response, Claim 1 has been amended. After entry of the instant amendment, Claims 1-9 are pending and under consideration.

II. AMENDMENT OF THE CLAIM

Amended Claim 1 recites a method for the detection of a nucleic acid comprising: (a)-producing a plurality of amplificates of a section of the nucleic acid by amplifying said section of nucleic acid with two primers, one of which binds to a first binding sequence A′ of one strand of the nucleic acid, wherein said binding sequence A′ is essentially complementary to a sequence A, located on the other strand of the nucleic acid, and the other primer binds to a second binding sequence C, which is located in the 3′ direction from A and does not overlap A, in the presence of a probe having a binding sequence D, wherein at least a portion of D is essentially complementary to all of sequence B, wherein sequence B consists of all the nucleotides between sequence A and binding sequence C, and wherein the probe has a reporter group and a quencher group, using a polymerase having 5′ nuclease activity; and (b)-detecting the nucleic acid by measuring a signal which is caused by the release of the reporter group, wherein the amplificates have a length of 75 nucleotides or less.

Support for amended Claim 1 can be found in the specification, at page 26, lines 9 to 21 (and Figure 3 as discussed therein). Therein is described the relative size of binding sequence B with the binding sequence of the probe, D. Binding sequence B is located between sequence A and binding sequence C (complementary binding sequence B′ is located between binding sequence A′ and sequence C′). Binding sequence D can be the length of sequence B, (page 26, lines 23 to 26 and Figure 3, I). Alternatively, binding sequence D can be longer than sequence B, extending into regions A and/or region C, as illustrated by Figure 3, II-IV, and described at page 26, lines 9 to 21. In addition, binding sequence D can further comprise additional groups or residues or nucleic acid binding regions as described at page 26, lines 2 to 7 and illustrated in Figure 3, V-VI. In all variations, at least a portion of D is essentially complementary to all of sequence B.

Applicants submit that the amended Claim 1 is fully supported by the specification and respectfully request entry thereof.

III. PRIORITY

A. Certified Copies of Translations of the Priority Applications

The PTO acknowledges Applicants claim to foreign priority of German applications DE 197 48 690.8, filed November 4, 1997 and DE 198 14 001.0, filed March 28, 1998 but states that a certified translation of these documents has not been received. Applicants claim priority to three German applications, as discussed below. Applicants submit herewith certified copies of a translation of each priority application, attached at Exhibit 1. Applicants respectfully request that the claim to foreign priority be granted.

B. Priority Applications

Applicants Declaration and Power of Attorney, submitted May 4, 2000, claims priority of three German applications under 35 U.S.C. § 119: DE 197 48 690.8, filed November 4, 1997, DE 198 14 001.0, filed March 28, 1998 and DE 198 14 828.3, filed April 2, 1998. Applicants submitted a Request for Correction of Filing Receipt on December 9, 2002, to correct the Foreign Applications portion as well as the Drawing Count and Title portions of the Filing Receipt. Applicants are awaiting a response to the Request for Correction of Filing Receipt. For the Examiner's convenience, a copy of the Declaration and Power of Attorney, submitted May 4, 2000, is attached at Exhibit 2 and a copy of the Request for Correction of Filing Receipt, submitted December 9, 2002, is attached at Exhibit 3. The Request for Correction of Filing Receipt was originally submitted with an Exhibit A and Exhibit B which are also included herewith.

IV. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-9 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite as to the recitations "wherein the amplificates have a length of 75 nucleotides or less, and the sequences located between the binding sequences A and C contains no nucleotides that do not belong to a sequence region E of the amplificate that is bound by binding sequence D of the probe" (antecedent basis) and "contains no nucleotides that do not belong to a sequence region E of the amplificate that is bound by binding sequence D of the probe" (sequence composition).

A. Claims 1-9, antecedent basis

Claims 1-9 stand rejected as allegedly indefinite for lack of antecedent basis as to "binding sequence A."

As discussed above, Applicants have amended Claim 1, without narrowing its scope, to remove recitation of binding sequence A. Amended Claim 1 recites, *inter alia*, that sequence B consists of all the nucleotides between sequence A and binding sequence C. Sequence B is located between sequence A and binding sequence C and the complement thereof, B′, is located between binding sequence A′ and sequence C′.

Applicants submit that amended Claims 1-9 are definite and respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

B. Claims 1-9, sequence composition

Claims 1-9 stand rejected as allegedly indefinite as to the recitation "contains no nucleotides that do not belong to a sequence region E of the amplificate that is bound by binding sequence D of the probe."

As discussed above, Applicants have amended Claim 1 to recite, in relevant part, a probe having a binding sequence D, wherein at least a portion of D is essentially complementary to all of sequence B, wherein sequence B consists of all the nucleotides between sequence A and binding sequence C. At least a portion of binding sequence D is essentially complementary to all the nucleotides of sequence B which consists of all the nucleotides between sequence A and binding sequence C′. Thus, amended Claims 1-9 are definite in that they recite the composition of the sequences between sequences A and C.

Applicants submit that amended Claims 1-9 are definite and respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

V. CLAIM REJECTION UNDER 35 U.S.C. §102

Claims 1-9 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Livak (U.S. Patent No. 6,154,707, "the '707 patent").

The '707 patent was filed June 3, 1999, as a divisional of a U.S. application filed February 4, 1998. Applicants filed the instant application on May 4, 2000, claiming priority to a PCT filed November 3, 1998 and three German applications filed November 4, 1997, March 28, 1998 and April 2, 1998. Applicants submit that the present application has a

priority date that is prior to the priority date of the '707 patent. Thus the '707 patent cannot anticipate Applicants' Claims 1-9.

Applicants submit that the '707 patent does not have a priority date prior to Applicants' application. Applicants submit that the '707 patent cannot anticipate Claims 1-9 and respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

VI. CLAIM REJECTION UNDER 35 U.S.C. §103

Claims 1-9 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Livak (U.S. Patent No. 5,538,848, "Livak") in view of Khan (U.S. Patent No. 5,948,648, "Khan"). Claims 1-9 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Livak (U.S. Patent No. 5,538,848) in view of Walker (1992, *Proc. Natl. Acad. Sci. USA* 89:392-96).

Khan was filed May 29, 1998. Applicants filed the instant application on May 4, 2000, claiming priority to a PCT filed November 3, 1998 and three German applications filed November 4, 1997, March 28, 1998 and April 2, 1998. Applicants submit that the present application has a priority date that is prior to the priority date of Khan. Thus Khan is not a valid reference in view of its priority date.

A. Legal Standard for Obviousness

To reject claims in an application under 35 U.S.C. §103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992).

In order to establish *prima facie* obviousness, three basic criteria must be met. First, when an obviousness rejection relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside* , 53 USPQ2d 1769 (Fed. Cir. 2000). If any one of three criteria are not met, *prima facie* obviousness is not established. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

B. The References

i. Livak

Livak teaches a method for monitoring the progress of nucleic acid amplifications that relies on a nucleic acid polymerase having 5′ to 3′ exonuclease activity. As acknowledged by the PTO, Livak does not teach or suggest a method for the detection of a nucleic acid wherein amplificates having a length of less than 75 nucleotides are produced from a section of the nucleic acid. In addition, Livak does not teach or suggest a probe having a binding sequence which is essentially complementary to at least all the nucleotides between sequence A and binding sequence C.

ii. Khan

As discussed above, Applicants submit that Kahn is not prior art.

iii. Walker

Walker teaches an isothermal strand displacement amplification method wherein the primers contain a recognition sequence for a restriction enzyme. Walker describes amplification of a 47 bp fragment with subsequent detection of product. Walker does not teach or suggest a method for contemporaneous detection of a nucleic acid wherein amplificates having a length of less than 75 nucleotides are produced from a section of the nucleic acid.

C. There is no Suggestion or Motivation to Combine Livak and Khan nor Livak and Walker as Cited by the PTO

Amended Claim 1 recites a method for the detection of a nucleic acid comprising producing 75 nucleotide or shorter amplificates of the nucleic acid using two primers, a polymerase have 5′ nuclease activity and a labeled probe sequence, and detecting a signal from label released from the probe, wherein at least a portion of binding sequence D is essentially complementary to all the nucleotides of sequence B wherein sequence B consists of all the nucleotides between the sequence A and binding sequence C. Claims 2-9 depend from amended Claim 1.

The PTO asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the teachings of Livak in view of Khan. The PTO states that Kahn's teaching of nucleoside/tide compound and its ability to produce small

amplificates, labeled with a first and second dye, on the order of less than 50 nucleotides would be added to the teaching of Livak to produce and detect amplicons of 61 bp or less. Applicants respectfully disagree.

As discussed above, Applicants submit that Kahn is not prior art. Therefore, one of skill in the art could not be motivated to combine the teachings of Livak in view of Kahn.

In addition, the PTO asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the teaching of Livak in view of Walker as the addition of restriction enzyme sites to the sequence of primers is well known in the art and would have been obvious to the practitioner of the Livak method in their attempt to detect small amplicons of 61 bp or less. Applicants respectfully disagree.

Neither Livak not Walker describe amplificates consisting of nucleotides between the primer binding sites, all of said nucleotides being complementary to the binding sequence of the probe. In addition, Walker teaches a heterogeneous amplification method, whereby the probe hybridization is conducted following amplification of the target. Therefore, one of skill in the art would not be motivated to combine the teachings of Livak in view of Walker.

D. <u>The References Cited by the PTO Fail to Teach Each and Every Element of Claims 1-9</u>

Applicants submit that the references cited by the PTO do not teach or suggest each and every element of Claim 1. In particular, the claimed method provides release of label from the probe during amplification of a 75 nucleotide or smaller amplificate, wherein at least a portion of the probe binding sequence D is essentially complementary to a region that consists of all the nucleotides between sequence A and binding sequence C. That is, the claimed method provides label release from a probe, at least a portion of the probe having a binding sequence essentially complementary to all of the nucleotides of sequence B which consists of all of the nucleotides between the primer binding sites A′ and C (*i.e.*, 75 nucleotides or shorter in length). As further taught by the specification, the probe binding sequence D may or may not overlap with the primer binding sites. (*See,* page 26 and Fig. 3I-VI). Neither Livak nor Walker, alone or in any combination, teaches or suggests Applicants' claimed method. Khan could not, alone or in any combination teach or suggest Applicants' claimed method.

E. Livak in view of Khan

Livak alone does not teach or suggest each and every element of Claims 1-9. Khan could not, alone or in any combination, teach or suggest each and every element of Claims 1-9.

As discussed above, Applicants submit that Khan is not prior art. Furthermore, Livak does not teach or suggest that a probe containing a reporter group can be degraded by the 5′ nuclease activity of a polymerase while the probe is bound to an amplificate having a length of less than 75 nucleotides.

Figure 1 of Livak, illustrates that the binding sequence of the probe (corresponding to Applicants' binding sequence D) is complementary to a sequence which consists of less than all the sequences between the forward and reverse primers, *i.e.* less than all the nucleotides between binding sequence A and C′. Figure 1 of Livak is generally depicted in Figure 3 VII of Applicants specification and described as prior art, page 14, lines 26 to 27. In Livak, the probe region (binding sequence D) is complementary to a sequence that consists of less than all the nucleotides between the forward and reverse primers binding sequences A′ and C (or the complements thereof, A and C′). Thus, Livak fails to teach or suggest a probe, wherein at least a portion of the probe is essentially complementary to all the nucleotides between sequence A and binding sequence C.

Based on the foregoing, Applicants respectfully submit that Livak does not teach or suggest each and every element of Applicants' Claims 1-9. Furthermore, Khan, alone or in combination could not teach or suggest each and every element of Applicants' Claims 1-9. Neither Livak nor Khan render Applicants' claimed method obvious. Applicants therefore request that the rejection of Claims 1-9 under 35 U.S.C. §103(a) be withdrawn.

F. Livak in view of Walker

As stated above, Livak fails to teach or suggest each and every element of Applicants' Claims 1-9. Livak fails to teach or suggest a probe that is complementary to all the nucleotides between the primer binding sequences.

Walker teaches an isothermal strand displacement amplification method wherein the primers contain a recognition sequence for a restriction enzyme. Walker describes amplification of a 47-bp fragment with subsequent detection of product. Walker does not teach or suggest a method for contemporaneous detection of a nucleic acid wherein amplificates having a length of less than 75 nucleotides are produced from a section of the

nucleic acid. In addition, Walker fails to teach or suggest a probe that is complementary to all the nucleotides between the primer binding sequences. Thus, Walker fails to teach or suggest each and every element of Applicants' Claims 1-9.

Applicants respectfully submit that Livak and Walker do not teach or suggest each and every element of Applicants' Claim 1-9. Neither Livak nor Walker render Applicants' claimed method obvious. Applicants therefore request that the rejection of Claims 1-9 under 35 U.S.C. §103(a) be withdrawn.

VII. CLAIM REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

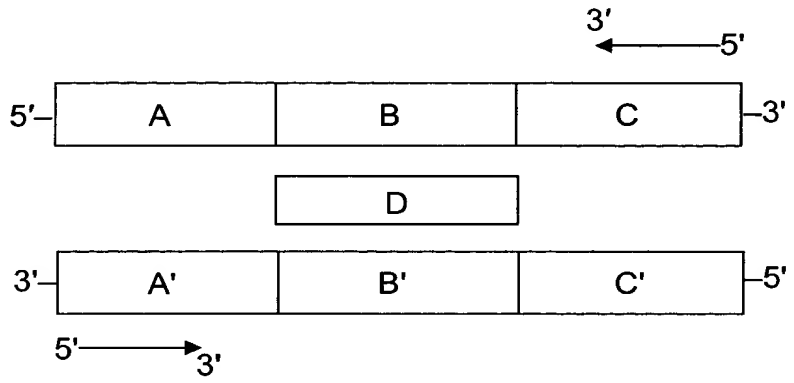
Claims 1-9 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing new matter. Applicants respectfully disagree. The subject matter of a claim need not be described literally (*i.e.*, using the same terms or in *haec verba*) in order for the disclosure to satisfy the description requirement. MPEP §2163.02. The specification must convey with reasonable clarity to those skilled in the art that, as of the filing date, he or she was in possession of the invention. *See, Vas-Cath Inc. v. Mahurkar* 935 F.2d 1555 (Fed. Cir. 1991).

Claim 1 is fully described in the specification as originally filed, *e.g.* Figure 2 and Examples 1-3. There were errors in a few portions of the specification as to labels A, A′, C and C′, which Applicants corrected in the last response to an Office Action, mailed March 27, 2003. However, the remainder of the specification conveyed to one skilled in the art that Applicants were in possession of the invention of Claim 1, even though some terminology may have been incorrect.

Figure 2 depicts the amplificate as comprising sequences A, B and C, wherein C is located in the 3′ direction of A. Also depicted is the complement of the amplificate comprising sequences A′, B′ and C′. To produce such an amplificate, the primers must bind to sequences A′ and C rather than A and C′ as now recited in amended Claim 1.

Examples 1-3 (page 41 to page 45) describe, *inter alia*, possible primer combinations and amplicons shown in Figures 6 and 7. At the top of Figure 6 is provided a HCV genomic sequence from region 261-333 (5′ to 3′). One of skill in the art will recognize that the complement to this HCV genomic sequence is a 3′ to 5′ strand. This complementary strand corresponds to the strand represented as 3′ - A′ / B′ / C′ - 5′ in Fig. 2, while the genomic sequence provided corresponds to the strand represented as 5′ - A/ B/ C - 3′ in Fig. 2. The forward primer CK10, for example, is provided on line 1 of Fig. 6

(5′-CGTACTGCCTGATAGGGTGCT-3′) and the reverse primer CK20 (3′-CAGAGMATMTGGMATCGTGTAMG-5′). One of skill in the art will recognize that the forward primer, CK10, can only bind to binding sequence A′ and reverse primer, CK20, can only bind to binding sequence C, as depicted below.



All the primers provided in Figs. 6 and 7 work in the same fashion; the forward primers binding to binding sequence A′ and the reverse primers bind to binding sequence C. The probes provided are essentially complementary to a binding sequence between binding sequences A′ and C as provided in the Examples and recited in amended Claim 1.

The Examples and Figures in the specification amply support Applicants amendment and do not introduce new matter. Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

VIII. RELATED APPLICATIONS

For the PTO's convenience, Applicants identify applications related to the currently pending matter.

Applicants have three pending applications related to the present application, provided below. U.S. Application No. 10/322,138 is a divisional application of U.S. Application No. 09/530,746.

U.S. Application No.	Filing Date	Attorney Docket No.
09/530,746	May 4, 2000	1803-277-999
09/530,929	May 4, 2000	1803-303-999
10/322,138	December 17, 2002	1803-356-999

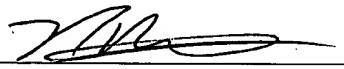
CONCLUSION

Applicants submit that Claims 1-9 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-9 to issuance is therefore kindly solicited.

No fees are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150 (Order No. 1803-302-999).

Respectfully submitted,

Date: September 4, 2003



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